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RESEARCH ARTICLE APPLIED MATHEMATICS

Modelling and Stability Analysis of (TIV) System Using Lyapunov Function

Ansaf Kh Faleh Alfkhakhari [1, *]

[1]Department of Mathematics, Faculty of Science, University of Derne, Derna, Libya

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A B S T R A C T

Tumour Immune Virus (TIV) model is theoretically analysed based on a system of five nonlinear ordinary differential equations (NODEs). The model is divided into five compartmental classes: uninfected cancer cells (U_x), virus-infected cancer cells (U_y), immune effector cells (U_z), dead cells (U_n), and free virus particles (U_v). The aim is to investigate the stability of the deterministic TIV model both analytically and numerically, utilising the Lyapunov function and the Runge-Kutta-Fehlberg (RKF) method. For the deterministic model, five steady points are derived, and their local and global stability are investigated for the coexistence steady point; however, specific criteria were employed to confirm the existence and stability of these steady states. Also, numerical simulations were conducted to study the dynamic behaviour of the TIV system, whose findings offer more insights into the impact of oncolytic treatment on the immune response and contribute to the development of more effective strategies.

نمذجة وتحليل استقرار نظام (TIV) باستخدام دالة ليابونوف

انصاف خيرالله فالح الفخاخري [*,1]

الكلمات المفتاحية

دالة ليابونوف
خطية النظام
تحليل الاستقرار
نموذج السرطان
العلاج الفيروسي للأورام

الملخص

تمت دراسة نموذج فيروس المناعة الورمية (TIV) وتحليله نظريًا استنادًا إلى نظام من خمس معادلات تفاضلية عادية غير خطية (NODEs). ينقسم النموذج إلى خمس فئات، هي: خلايا سرطانية غير مصابة (U_x)، وخلايا سرطانية مصابة بالفيروسات (U_y)، وخلايا مناعية فعالة (U_z)، وخلايا ميتة (U_n)، وجزيئات فيروسية حرة (U_v). يهدف هذا البحث بشكل أساسي إلى دراسة استقرار نموذج (TIV) الحتمي تحليليًا وعدديًا، باستخدام دالة ليابونوف وطريقة رونج-كوتا-فيلبرج (RKF). بالنسبة للنموذج الحتمي، تم الحصول علي خمس نقاط استقرار، ودُرست استقراريتها المحلية والعالمية لنقطة الاستقرار المشتركة. بالإضافة إلى ذلك، استُخدمت معايير محددة لتأكيد وجود واستقرار هذه الحالات المستقرة. أُجريت محاكاة عددية باستخدام الطريقة العددية المذكورة لتوضيح السلوك الديناميكي للنظام. توفر هذه النتائج رؤى أعمق حول تأثير العلاج الحالي للأورام على آليات الجهاز المناعي وتساهم في تطوير استراتيجيات تحكم أكثر فعالية وقائمة على الأدلة.

Introduction

In recent years, mathematical models have been used to understand and predict the dynamics of virotherapy for cancer. Among the models presented, there are simple models focused only on the interactions between uninfected and infected cancer cells, in addition to more complex ones that incorporate immune responses, free viral populations, and a combined treatment strategy, such as radiotherapy. Wodarz assumed logistic tumour growth and direct interactions between infected and uninfected cells, later including free virus dynamics [1]. Although this model omitted virus depletion due to cancer cell infection, this was later addressed by Bajzer et al.; also several stable points were obtained, and the Hopf bifurcation was analysed under specific criteria [2]. Al-Tuwairqi et al. determined tumour growth logistic by focusing on injectable viral dynamics and virus depletion. Combining radiotherapy with viral therapy improves cancer elimination when non-radioactive cells are damaged faster than they proliferate [3]. Renuka et al. proposed a four-equation model comprising a cancer cell, an infected cancer cell, a dead cell, and unrelated viruses, as well their parameters sensitivity study to know how to affect the system dynamics, providing insights for treatment optimization [4]. These advances in virotherapy modelling demonstrate an improvement towards greater biological reality, including: logistic growth for long-term studies, immune interactions, accurate accounting of free-virus fate post-infection, and research into combined therapies [5]. This dynamic framework serves as a basis for the current investigation. We will observe the cancer viro-immunotherapy model [6], which employs the human immune system to attack tumour cells through viruses. We use ordinary differential equations (ODEs) to perform Lyapunov stability analysis on the

*Corresponding author
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coexistence steady point in the TIV model, which provide a mathematical framework for examining the stability of dynamical systems [7]. The Lyapunov function is an important mathematical tool for analyzing TIV models to ensure their stability and accuracy [8].

As a result, mathematical models of cancer cells can be used to assess their long-term behaviours and the stability of their steady state. This study also uses numerical methods to simulate the TIV model and obtain accurate approximate solutions, such as the Runge-Kutta (RK) method, providing new understandings into disease dynamics and enabling the development of more effective strategies [9]. The paper for TIV model is organized as follows: Section 2 introduces the TIV model, and presents the existence of steady points. Section 3 analyses the stability of steady points locally and the global stability of the coexistence steady point. Section 4 provides numerical simulations using MATLAB and the RKF method, and also discusses the biological implications of the stability results. Finally, Section 5 concludes the paper.

The Model

The TIV mathematical model describes the interactions between cancer cells uninfected U_x and infected by virus U_y, immune effector cells U_z, dead cells U_n, and viral particles U_v in this section. Based on NODEs, the model captures the essential biological processes. In **Table 1**, five state variables are summarised by biologically meaningful interactions represented by proliferation, immune response, cell death, and viral dynamics.

Table 1: The description of the state variables of TIV model

Variable	Description
$\boldsymbol{U_x(t)}$	Uninfected cancer cells
$\boldsymbol{U_y(t)}$	Infected cancer cells by virus
$\boldsymbol{U_z(t)}$	Immune effector cells
$\boldsymbol{U_n(t)}$	Dead cancer cells
$\boldsymbol{U_v(t)}$	Free oncolytic virus particles

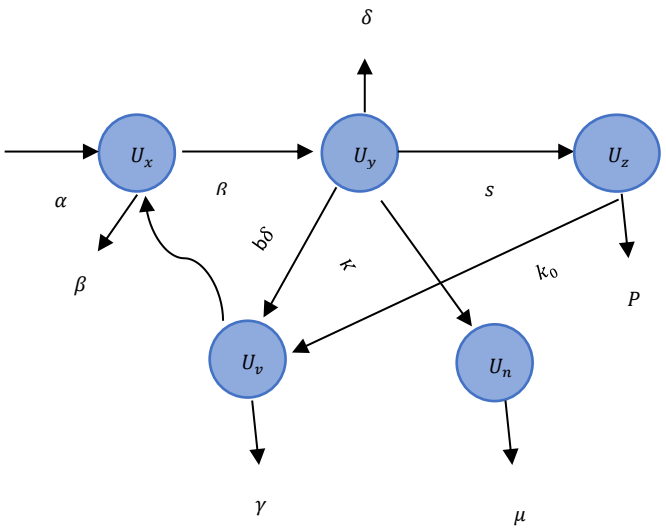

Figure 1: Flow chart describe the interaction between cells (U_x, U_y, U_z, U_n) and viruses (U_v)

Therefore, the TIV model is mathematically formulated as [6]:

$$\frac{dU_x(t)}{dt} = \alpha\, U_x(t) - \beta U_x(t) U_v(t) \quad (1)$$

$$\frac{dU_y(t)}{dt} = \beta U_x(t) U_v(t) - kU_y(t) U_z(t) - \delta U_y(t) \quad (2)$$

$$\frac{dU_z(t)}{dt} = sU_y(t) U_z(t) - \omega U_z^2(t) - PU_z(t) \quad (3)$$

$$\frac{dU_n(t)}{dt} = kU_y(t) U_z(t) + \delta U_y(t) - \mu U_n(t) \quad (4)$$

$$\frac{dU_v(t)}{dt} = b\delta U_y(t) - k_0 U_v(t) U_z(t) - \gamma U_v(t) \quad (5)$$

Initial conditions for TIV system:

$U_x(t_0) = U_{x_0},\ \mathrm{U}_y(t_0) = U_{y_0},\ \mathrm{U}_z(t_0) = U_{z_0},\ \mathrm{U}_n(t_0) = U_{n_0},\ \mathrm{U}_v(t_0) = U_{v_0}, t_0 \geq 0$

The TIV model is based on the following biological assumptions [12]:

- Uninfected cancer cells U_x proliferate with a constant growth rate α. This growing is reduced from the infection by free virus U_v at term $\beta\, U_x(t)\, U_v(t)$.
- viruses U_v infect cancer cells U_x, producing infected cancer cells U_y demonstrate at term $\beta\, U_x(t)\, U_v(t)$.
- Infected cancer cells U_y die naturally at rate δ and are eliminated by immune effector cells U_z at term $k\, U_y(t)\, U_z(t)$.
- Immune effector cells are stimulated by infected cancer cells at term $s\, U_y(t)\, U_z(t)$. Their number is reduced due to immune exhaustion and clearance, represented by the quadratic term $\omega\, U_z^2(t)$, as well as suppression effects modelled by the parameter P.
- Dead cancer cells U_n arise from both immune killing and natural death of infected cells. These dead cells are removed from the system at a constant clearance rate μ.
- Oncolytic viruses U_v are released with the death of infected cancer cells, with a burst size described by the parameter b. Free virus particles are eliminated through immune cell uptake at term $k_0\, U_v(t)\, U_z(t)$ and natural degradation at rate γ.

Theorem 1: Existence and Uniqueness of Solutions of TIV Model

Let $\Psi = \left(U_x, U_y, U_z, U_n, U_v\right) \in \mathbb{R}_+^5$ be the biologically relevant domain. Then for any initial conditions $\left(U_{x_0}, U_{y_0}, U_{z_0}, U_{n_0}, U_{v_0}\right) \in \Psi$, there exists a unique solution $\left(U_x(t), U_y(t), U_z(t), U_n(t), U_v(t)\right)$ of the TIV model (1) - (5) for all $t \geq 0$ [10].

Proof Define the vector field F: $\mathbb{R}^5 \to \mathbb{R}^5$:

$$F_1\left(U_x, \mathrm{U}_y, \mathrm{U}_z, \mathrm{U}_n, \mathrm{U}_v\right) = \alpha\, U_x - \beta\, U_x\, U_v \quad (6)$$

$$\mathrm{F}_2\left(U_x, \mathrm{U}_y, \mathrm{U}_z, \mathrm{U}_n, \mathrm{U}_v\right) = \beta U_x U_v - kU_y U_z - \delta\, U_y \quad (7)$$

$$F_3\left(U_x, \mathrm{U}_y, \mathrm{U}_z, \mathrm{U}_n, \mathrm{U}_v\right) = s\, U_y\, U_z - \omega\, \mathrm{U}_z^2 - P\, U_z \quad (8)$$

$$\mathrm{F}_4\left(U_x, \mathrm{U}_y, \mathrm{U}_z, \mathrm{U}_n, \mathrm{U}_v\right) = k\, U_y\, U_z + \delta\, U_y - \mu\, U_n \quad (9)$$

$$F_5(U_x, U_y, U_z, U_n, U_v) = b\,\delta\,U_y - k_0\,U_v\,U_z - \gamma\,U_v \quad (10)$$

Where $\alpha, \beta, k, \delta, s, \omega, P, \mu, b, k_0, \gamma$ are positive constants.

Step 1: Local Lipschitz Continuity

Since each component F_i is a polynomial function of the variables U_x, U_y, U_z, U_n, U_v. Hence, $F \in C^1(\mathbb{R}^5)$. Consider any compact set $K \subset \Psi$.

There exists $M > 0$ such that:

$0 \le U_x, U_y, U_z, U_n, U_v \le M$, for all $(U_x, U_y, U_z, U_n, U_v) \in K$.

The Jacobian matrix $J = DF(U_x, U_y, U_z, U_n, U_v)$ of the TIV system is:

$$J = \begin{pmatrix} \alpha - \beta U_v & 0 & 0 & 0 & -\beta U_x \\ \beta U_v & -kU_z - \delta & -kU_y & 0 & \beta U_x \\ 0 & sU_z & sU_y - 2\omega U_z - P & 0 & 0 \\ 0 & kU_z + \delta & kU_y & -\mu & 0 \\ 0 & b\delta & -k_0 U_v & 0 & -k_0 U_z - \gamma \end{pmatrix},$$

where $J \in \mathbb{R}^{5\times 5}$

Since all variables are bounded on K, all partial derivatives of F are bounded on K. Therefore, there exists a constant $L > 0$ such that:

$$\|DF(X)\| \le L, \text{ for all } X \in K.$$

Using the mean value theorem for (1) – (5) system, we get:

$$\| F(X) - F(Y) \| \le L \| X - Y \| \text{for all } X, Y \in K.$$

Hence, F is locally Lipschitz continuous on Ψ.

Step 2: Local Existence and Uniqueness of TIV model

By the Picard–Lindelöf theorem [11], for any initial condition

$$(U_{x_0}, U_{y_0}, U_{z_0}, U_{n_0}, U_{v_0}) \in \Psi,$$

There exists a unique local solution $(U_x(t), U_y(t), U_z(t), U_n(t), U_v(t))$ of the TIV system (1) – (5) defined on some interval $[0, T), T > 0$.

Step 3: Proving positive invariance of Ψ.

Lemma 1:

The set Ψ is positively invariant.

Proof We study the system on the boundary of $\partial\Psi$.

If $U_x = 0$, then $U_x^{\cdot} = 0$.

If $U_y = 0$, then $U_y^{\cdot} = 0$.

If $U_z = 0$, then $U_z^{\cdot} = 0$.

If $U_n = 0$, then $U_n^{\cdot} = 0$.

If $U_v = 0$, then $U_v^{\cdot} = 0$.

Therefore, the vector field F fails to point toward the outside on the boundary of $\partial\Psi$. Assume, by contradiction, that a solution becomes negative at the beginning, $t_0 > 0$. At this point, the corresponding variable's derivative must be negative at zero, which contradicts the previously provided boundary analysis. Solutions starting with Ψ remain in Ψ for all $t \ge 0$.

Step 4: Global Existence on $[0, \infty)$

Lemma 2:

Define the total number function $U(t)$ for TIV model, such that:

$$U(t) = U_x(t) + U_y(t) + U_z(t) + U_n(t) + U_v(t) \quad (11)$$

Compute the derivative of equation (11):

$$\begin{aligned} \frac{dU}{dt} = \frac{dU_x}{dt} + \frac{dU_y}{dt} + \frac{dU_z}{dt} + \frac{dU_n}{dt} + \frac{dU_v}{dt} \\ = (\alpha U_x - \beta U_x U_v) \\ + (\beta U_x U_v - kU_y U_z - \delta U_y) \\ + (sU_y U_z - \omega U_z^2 - PU_z) \\ + (kU_y U_z + \delta U_y - \mu U_n) \\ + (b\delta U_y - k_0 U_v U_z - \gamma U_v) \end{aligned} \quad (12)$$

Thus,

$$\begin{aligned} \frac{dU}{dt} = \alpha U_x - \omega U_z^2 - PU_z - \mu U_n - \gamma U_v \\ + (b\delta - \delta) U_y \end{aligned} \quad (13)$$

Since all parameters are positive and b, δ are bounded, we get:

$$\frac{dU}{dt} \le \alpha U_x + C \le \alpha U + C \quad (14)$$

for some constant $C > 0$.

By Grönwall's inequality:

$$U(t) \le \left(U(0) + \frac{C}{\alpha}\right) e^{\alpha t} - \frac{C}{\alpha} \quad (15)$$

Thus, $U(t)$is bounded on every finite interval. Therefore, the solution can be extended for all $t \ge 0$, and

$$T_{Max} = \infty.$$

Hence, the TIV model (1) – (5) has a unique global solution $(U_x(t), U_y(t), U_z(t), U_n(t), U_v(t))$ for any initial condition in Ψ [10].

Theorem 2:

The TIV model (1) – (5) has exactly five steady points in $\mathbb{R}^5$, which are classified as follows:

- There are three biologically relevant steady states.
- The existence of two steady points that are biologically irrelevant.

Where all parameters of the TIV model $\alpha, \beta, k, \delta, s, \omega, P, \mu, b, k_0, \gamma > 0$ [12].

Proof For each variable U_x, U_y, U_z, U_n, U_v in the TIV model (1) - (5), set the derivative to zero. Solve the resulting system of equations to get the values of the variables U_x, U_y, U_z, U_n, and U_v at which the system is in steadiness [13]. We obtain the following five steady points:

$E_0 = (0,0,0,0,0)$

$E_1 = \left(0,0,-\frac{P}{\omega},0,0\right)$

$$E_2 = \left(0, \frac{kP - \omega\delta}{ks}, -\frac{\delta}{k}, 0, \frac{-\left(b\delta(kP - \delta\omega)\right)}{s(\delta k_0 - k\gamma)}\right)$$

$$E_3 = \left(\frac{\gamma}{\beta b}, \frac{\gamma\alpha}{\mu\beta b}, 0, \frac{\gamma\alpha}{\mu\beta b}, \frac{\alpha}{\beta}\right)$$

$E_4 = \left(U_x^*, U_y^*, U_z^*, U_n^*, U_v^*\right)$, where:

$$U_x^* = \frac{k_0 P(\delta(b\beta kP + \alpha s k_0) - \alpha k s\gamma) - \omega(\delta(\beta b(P(\delta k_0 - k\gamma) + \delta\gamma\omega) - \alpha s\gamma k_0) + \alpha k s\gamma^2)}{(\alpha k_0 s - b\beta\delta\omega)^2},$$

$$U_y^* = \frac{\alpha(Pk_0 - \gamma\omega)}{\alpha k_0 s - b\beta\delta\omega}, \quad U_z^* = \frac{Pb\beta\delta - \alpha\gamma s}{\alpha k_0 s - b\beta\delta\omega},$$

$$U_n^* = \frac{\alpha(Pk_0 - \gamma\omega)(\alpha\delta k_0 s - \alpha\gamma k s - b\beta\delta^2\omega + Pb\beta\delta k)}{(\mu(\alpha k_0 s - b\beta\delta\omega)^2)},$$

$$U_v^* = \frac{\alpha}{\beta}.$$

E_0 represents a free steady point where all cells and viruses tend to zero, i.e., $U_x = U_y = U_z = U_n = U_v = 0$. The steady state E_1 is where the cancer cells U_x, U_y, the virus particles U_v, and the dead cells U_n have all been eliminated, and this steady point is biologically irrelevant. Similarly, E_2 is a steady point, representing the uninfected cancer cells U_x, and the dead cells U_n have been eliminated from the system, and this point is biologically irrelevant since $U_z < 0$. Also, the steady point E_3 is a tumour-dominated steady state, which represents the failed immune response state, which is a situation in which cancer cells U_x, U_y (both uninfected and infected) and oncolytic virus particles U_v remain in the body, but the immune system is suppressed or eliminated ($U_z = 0$). As for E_4 representing the co-existence steady point where all populations in an endemic steady state, it is biologically relevant only if: $U_x, U_y, U_z, U_n > 0$ [16].

Stability Analysis

This section presents the linearization of the system (1) - (5) and analyzes some biological steady points [13]. By identifying these conditions, we can better understand the long-term behaviour of the system (1) - (5). We first define the state vector of the TIV system as:

$$X(t) = \left(U_x(t), U_y(t), U_z(t), U_n(t), U_v(t)\right)^T \tag{16}$$

And let the vector X^* represent the generic steady-state point to the TIV model (1) – (5), as:

$$X^* = \left(\overline{U}_x, \overline{U}_y, \overline{U}_z, \overline{U}_n, \overline{U}_v\right)^T,$$

We will define the deviations from steady state as:

$$E(t) = X(t) - X^* \tag{17}$$

The nonlinear system (6) – (10) can be written in vector form as:

$$X^{\cdot}(t) = F\left(X(t)\right) \tag{18}$$

where:

$$F(X) = \left(F_1(X), F_2(X), F_3(X), F_4(X), F_5(X)\right)^T.$$

Since $X^*$is a generic steady point of the TIV system, then: $F(X^*) = 0$.

By applying the first-order Taylor expansion about F^*, we get:

$$F\left(X(t)\right) \approx F(X^*) + \frac{\partial F}{\partial X}|_X (X(t) - X^*) \tag{19}$$

Here: $\frac{\partial f}{\partial x}|_X = P$, represent the Jacobian matrix of $F = [F_1, F_2, F_3, F_4, F_5]^T$ with respect to the $X(t)$, calculated at X^*, which is:

$$P = \begin{bmatrix} \frac{\partial F_1}{\partial U_x} & 0 & 0 & 0 & \frac{\partial F_1}{\partial U_v} \\ \frac{\partial F_2}{\partial U_x} & \frac{\partial F_2}{\partial U_y} & \frac{\partial F_2}{\partial U_z} & 0 & \frac{\partial F_2}{\partial U_v} \\ 0 & \frac{\partial F_3}{\partial U_y} & \frac{\partial F_3}{\partial U_z} & 0 & 0 \\ 0 & \frac{\partial F_4}{\partial U_y} & \frac{\partial F_4}{\partial U_z} & \frac{\partial F_4}{\partial U_n} & 0 \\ 0 & \frac{\partial F_5}{\partial U_y} & \frac{\partial F_5}{\partial U_z} & 0 & \frac{\partial F_5}{\partial U_v} \end{bmatrix},$$

where $P \in \mathbb{R}^{5\times5}$

Then, the linearized TIV system around the steady point X^*can be written as:

$$\frac{dE(t)}{dt} = PE(t) \tag{20}$$

To analyze the stability of this linearized system (20), we consider an exponential solution of the form:

$E(t) = e^{t\lambda}\,\Upsilon, \Upsilon\ is$ nonzero vector.

Substituting into the equation (20), we get:

$$\lambda\, e^{\lambda t}\Upsilon = Pe^{\lambda t}\Upsilon$$

Divide both sides by $e^{\lambda t}$, we get:

$$\lambda\,\Upsilon = P\Upsilon$$

We can write it as:

$$(\lambda I - P)\Upsilon = 0$$

Given a non-vector $\Upsilon \in \mathbb{R}^5$, so:

$$det(\lambda I - P) = 0 \tag{21}$$

The equation (21) describes the characteristics of the system (1) – (5). In consequence, the stability of the steady points depends on the roots λ of this equation. It is locally asymptotically stable if all roots (λ) satisfy $Re(\lambda) < 0$.

Local Stability

The local stability of the steady points for the TIV model is investigated using the linearization method. Briefly, this method involves evaluating the Jacobian matrix $J = DF\left(U_x, U_y, U_z, U_n, U_v\right)$ of the TIV system around the biological steady point, and then proving that its eigenvalues are negative.

Theorem 3:

The free steady point E_0 is not locally asymptotically stable.

Proof The Jacobian matrix around the total extinction steady point E_0 is given as:

$$\mathrm{J}(0,0,0,0,0) = \begin{bmatrix} \alpha & 0 & 0 & 0 & 0 \\ 0 & -\delta & 0 & 0 & 0 \\ 0 & 0 & -P & 0 & 0 \\ 0 & \delta & 0 & -\mu & 0 \\ 0 & b\delta & 0 & 0 & -\gamma \end{bmatrix}$$

The eigenvalues around the free steady point are given as follows:

$$\lambda_1 = \alpha,\ \ \lambda_2 = -\delta,\ \ \lambda_3 = -P,\ \ \lambda_4 = -\mu,\ \ \lambda_5 = -\gamma.$$

Clearly, the eigenvalue λ_1 is positive. Hence, E_0 is not locally asymptotically.

Theorem 4:

The tumor- dominated steady state $E_3 = \left(\frac{\gamma}{\beta b}, \frac{\gamma\alpha}{\mu\beta b}, 0, \frac{\gamma\alpha}{\mu\beta b}, \frac{\alpha}{\beta}\right)$ is not locally asymptotically stable.

Proof The Jacobian matrix of the TIV system about the tumor- dominated steady point $\left(\frac{\gamma}{\beta b}, \frac{\gamma\alpha}{\mu\beta b}, 0, \frac{\gamma\alpha}{\mu\beta b}, \frac{\alpha}{\beta}\right)$ is as follow:

$$J(E_3) = \begin{bmatrix} \alpha - \beta U_v & 0 & 0 & 0 & -\beta U_x \\ \beta U_v & -\delta & -kU_y & 0 & \beta U_x \\ 0 & 0 & sU_y - P & 0 & 0 \\ 0 & \delta & kU_y & -\mu & 0 \\ 0 & b\delta & -k_0 U_v & 0 & -\gamma \end{bmatrix}$$

The characteristic polynomial of the TIV system corresponding to the steady point (E_3) is:

$$|J(E_3) - \lambda I| = 0,$$

We obtain the eigenvalues:

$\lambda_1 = \frac{s\gamma\alpha}{\mu\beta b} - P$, $\lambda_2 = -\mu$, and $\lambda_{3,4,5}$ satisfy the equation

$$\lambda^3 + (\gamma + \delta)\lambda^2 + \alpha\delta\gamma = 0,$$

where:

$a_1 = \gamma + \delta,$

$a_2 = 0,$

$a_3 = \alpha\delta\gamma,$

Now by applying Routh-Hurwitz criteria [15], if $a_1 > 0, a_3 > 0$, and $a_1 a_2 > a_3$ then the eigenvalues $\lambda_{3,4,5} < 0$ [4]. Obviously, $a_1, a_3 > 0$, but $a_1 a_2 < a_3$. Hence, the tumor-dominated steady state E_3 is not locally asymptotically stable.

Theorem 5:

The co-existence steady point $E_4 = \left(U_x^*, U_y^*, U_z^*, U_n^*, U_v^*\right)$ is locally asymptotically stable only if $a_1, a_3, a_4 > 0$, and $a_1 a_2 a_3 > a_3^2 + a_1^2 a_4$. a_1, a_2, a_3, and a_4 are provided in the proof [3].

Proof The Jacobian matrix of (1) – (5) system around E_4 is given as:

$$J\left(U_x^*, U_y^*, U_z^*, U_n^*, U_v^*\right) = \begin{bmatrix} \alpha - \beta U_v^* & 0 & 0 & 0 & -\beta U_x^* \\ \beta U_v^* & kU_z^* - \delta & -kU_y^* & 0 & \beta U_x^* \\ 0 & sU_z^* & sU\_y^* - 2\omega U_z^* - P & 0 & 0 \\ 0 & kU_z^* + \delta & kU_y^* & -\mu & 0 \\ 0 & b\delta & -k_0 U_v^* & 0 & -k_0 U_z^* - \gamma \end{bmatrix}$$

where we have used $\alpha - \beta U_v^* = 0$ since $U_v^* = \frac{\alpha}{\beta}$.

$$J\left(U_x^*, U_y^*, U_z^*, U_n^*, \frac{\alpha}{\beta}\right) = \begin{bmatrix} 0 & 0 & 0 & 0 & -\beta U_x^* \\ \alpha & kU_z^* - \delta & -kU_y^* & 0 & \beta U_x^* \\ 0 & sU_z^* & sU_y^* - 2\omega U_z^* - P & 0 & 0 \\ 0 & kU_z^* + \delta & kU_y^* & -\mu & 0 \\ 0 & b\delta & -k_0\frac{\alpha}{\beta} & 0 & -k_0 U_z^* - \gamma \end{bmatrix}$$

Thus, solving the characteristic equation $\left|J\left(U_x^*, U_y^*, U_z^*, U_n^*, \frac{\alpha}{\beta}\right) - \lambda I\right| = 0$, we obtain the eigenvalues:

$\lambda_4 = -\mu < 0,$

$$P_4(\lambda) = \det(\Lambda - \lambda I) = \lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4$$

where:

$$\Lambda = \begin{bmatrix} 0 & 0 & 0 & -\beta U_x^* \\ \alpha & kU_z^* - \delta & -kU_y^* & \beta U_x^* \\ 0 & sU_z^* & sU_y^* - 2\omega U_z^* - P & 0 \\ 0 & b\delta & -k_0\frac{\alpha}{\beta} & -k_0 U_z^* - \gamma \end{bmatrix}$$

By the Routh–Hurwitz conditions for a quartic require, if: $a_1 > 0, a_3 > 0, a_4 > 0$, and $a_1 a_2 a_3 > a_3^2 + a_1^2 a_4$.

Then the eigenvalues of $P_4(\lambda)$ have negative real parts [14].

Now: the coefficient of (λ^3):

$$a_1 = -trace(\Lambda) = -kU_z^* + \delta - sU_y^* + 2\omega U_z^* + P + k_0 U_z^* + \gamma$$

The coefficient of (λ^2):

$$a_2 = \sum \text{principal minors of order 2 of } (\Lambda) =$$

$$= \left(sU_y^* - 2\omega U_z^* - P\right)\left((k - k_0 U_z^* - \delta - \gamma)\right) + (kU_z^* - \delta)(-k_0 U_z^* - \gamma) - (b\delta\beta U_x^*) + kU_y^* sU_z^*$$

The coefficient of (λ):

$$a_3 = -\sum \text{principal minors of order 3 of } (\Lambda) =$$

$$= -\alpha\beta U_x^* (sU_z^* + b\delta) - s\,U_z^* \left[kU_y^*(k_0 U_z^* + \gamma) + \beta U_x^* k_0 U_v^*\right] + \left(sU_y^* - 2\omega U_z^* - P\right)\left[(kU_z^* - \delta)(k_0 U_z^* + \gamma) + \beta U_x^* b\delta\right],$$

The coefficient (a_4):

$$a_4 = det(\Lambda) = -\alpha^2 k_0 s U_z^* U_x^* - \alpha\beta U_x^* b\delta\left(sU_y^* - 2\omega U_z^* - P\right)$$

Therefore, if a_1, a_2, a_3, and a_4 are positive and satisfy the Routh-Hurwitz condition

$$a_1 a_2 a_3 > a_3^2 + a_1^2 a_4,$$

Consequently, all roots of the characteristic polynomial $P_4(\Lambda)$ have negative real parts. As a result, the coexistence steady point E_4 is locally asymptotically stable.

Global Stability

In this section, we use Lyapunov function analysis to prove the global stability of the co-existence steady point of TIV model. We know that $X^* = \left(\bar{U}_x, \bar{U}_y, \bar{U}_z, \bar{U}_n, \bar{U}_z\right)$, a generic steady-state solution to the cancer model (1) – (5), define the deviations from steady state as:

$U_x(t) - \bar{U}_x,\ U_y(t) - \bar{U}_y,\ U_z(t) - \bar{U}_z, U_n(t) - \bar{U}_n,\ U_v(t) - \bar{U}_v$

Theorem 6:

The coexistence steady point $E_4 = \left(\bar{U}_x, \bar{U}_y, \bar{U}_z, \bar{U}_n, \bar{U}_z\right)$, is globally stable in the biologically feasible region Ψ if the following parametric conditions hold:

(i) $s\bar{U}_y \le 2\omega\bar{U}_z + P$

(ii) $k_0\bar{U}_z + \gamma \ge \beta\bar{U}_x$

(iii) $b\delta \le m_i U_n(\frac{k\bar{U}_y\bar{U}_z}{\bar{U}_x}, \frac{\mu\bar{U}_n}{\bar{U}_y})$

(iv)$\alpha = \beta\bar{U}_z$

Proof Consider the following Lyapunov function:

$$L(U_x, U_y, U_z, U_n, U_v) = \left(U_x - \bar{U}_x - \bar{U}_x ln\frac{U_x}{\bar{U}_x}\right) + \left(U_y - \bar{U}_y - \bar{U}_y ln\frac{U_y}{\bar{U}_y}\right) + m_1\left(U_z - \bar{U}_z - \bar{U}_z ln\frac{U_z}{\bar{U}_z}\right) + m_2\left(U_n - \bar{U}_n - \bar{U}_n ln\frac{U_n}{\bar{U}_n}\right) + m_3\left(U_v - \bar{U}_z - \bar{U}_z ln\frac{U_v}{\bar{U}_z}\right)$$

Where: $m_i > 0, i = 12{,}3.$

For all $U > 0$, the function $U - \bar{U} - \bar{U} ln\frac{U}{\bar{U}} \ge 0 \Leftrightarrow (U = U').$

Hence,

$$L(U_x, U_y, U_z, U_n, U_v) \ge 0, L = 0 \Leftrightarrow (\bar{U}_x, \bar{U}_y, \bar{U}_z, \bar{U}_n, \bar{U}_z) = \mathrm{E}_4.$$

Therefore, L is positive definite.

The derivative of each term is given by:

$$\frac{d}{dt}\left(U - \bar{U} - \bar{U} ln\frac{U}{\bar{U}}\right) = \left(1 - \frac{\bar{U}}{U}\right)U'$$

$$L' = \left(1 - \frac{\bar{U}_x}{U_x}\right)U_x' + \left(1 - \frac{\bar{U}_y}{U_y}\right)U_y' + m_1\left(1 - \frac{\bar{U}_z}{U_z}\right)U_z' + m_2\left(1 - \frac{\bar{U}_n}{U_n}\right)U_n' + m_3\left(1 - \frac{\bar{U}_z}{U_v}\right)U_v'$$

Thus,

Substituting the TIV system (1) – (5):

$$L' = \left(1 - \frac{\bar{U}_x}{U_x}\right)(\alpha U_x - \beta U_x U_v) + \left(1 - \frac{\bar{U}_y}{U_y}\right)(\beta U_x U_v - kU_y U_z - \delta U_y) + m_1\left(1 - \frac{\bar{U}_z}{U_z}\right)(sU_y U_z - \omega U_z^2 - PU_z) + m_2\left(1 - \frac{\bar{U}_n}{U_n}\right)(kU_y U_z + \delta U_y - \mu U_n) + m_3\left(1 - \frac{\bar{U}_z}{U_v}\right)(b\delta U_y - k_0 U_v U_z - \gamma U_v)$$

Using steady condition. At E_4, the following hold:

$$\alpha = \beta\bar{U}_z,$$

$$\beta\bar{U}_x\bar{U}_z = k\bar{U}_y\bar{U}_z + \delta\bar{U}_y$$

$$s\bar{U}_y\bar{U}_z = \omega{\bar{U}_z}^2 + P\bar{U}_z$$

$$k\bar{U}_y\bar{U}_z + \delta\bar{U}_y = \mu\bar{U}_n$$

$$b\delta\bar{U}_y = k_0\bar{U}_z\bar{U}_z + \gamma\bar{U}_z$$

After substituting the steady conditions and the chosen constants m_1, m_2, m_3, we have:

$$L' = -\beta\,\bar{U}_x\,\bar{U}_z\left(2 - \frac{\bar{U}_x}{U_x} - \frac{U_x}{\bar{U}_x}\right) - \delta\bar{U}_y\left(2 - \frac{\bar{U}_y}{U_y} - \frac{U_y}{\bar{U}_y}\right) - \frac{k}{s}\omega(U_z - \bar{U}_z)2 - \delta\left(2 - \frac{\bar{U}_n}{U_n} - \frac{U_n}{\bar{U}_n}\right) - \frac{\beta\bar{U}_x\gamma}{b\delta}\left(2 - \frac{\bar{U}_z}{U_v} - \frac{U_v}{\bar{U}_z}\right) + R(U_x, U_y, U_z, U_n, U_v)$$

where $R(U_x, U_y, U_z, U_n, U_v)$ contains interaction terms that must be non-positive. Ensuring Non-Positivity Under Conditions (i) - (iii):

(i) $s\bar{U}_y \le 2\omega\bar{U}_z + P$

(ii) $k_0\bar{U}_z + \gamma \ge \beta\bar{U}_x$

(iii) $b\delta \le m_i U_n(\frac{k\bar{U}_y\bar{U}_z}{\bar{U}_x}, \frac{\mu\bar{U}_n}{\bar{U}_y})$

Under these conditions, we can show:

$$L' \le -\beta\bar{U}_x\bar{U_v}\frac{(U_x - \bar{U}_x)^2}{U_x\bar{U}_x} - \delta\bar{U}_y\frac{(U_y - \bar{U}_y)^2}{U_y\bar{U}_y} - \frac{k\omega}{s}(U_z - \bar{U}_z)^2 - \frac{\delta(U_n - \bar{U}_n)^2}{U_n\bar{U}_n} - \frac{\frac{\beta\bar{U}_x\gamma}{b\delta}(U_v - \bar{U}_z)^2}{U_v\bar{U}_z}$$

Since all parameters are positive and $U_x, U_y, U_z, U_n, U_v > 0$ in Ψ. Collecting terms, we obtain:

$L' \le 0$ for all $(U_x, U_y, U_z, U_n, U\_v) \in \Psi$.

Moreover, $L' = 0 \Leftrightarrow (\bar{U}_x, \bar{U}_y, \bar{U}_z, \bar{U}_n, \bar{U}_z) = E_4$.

Thus, the largest invariant set contained in $\{(U_x, U_y, U_z, U_n, U_v) \in \Psi: L' = 0\}$ is E_4.

Hence, by LaSalle's Invariance Principle, the coexistence steady point E_4 is globally asymptotically stable in Ψ [13].

Numerical Validation of Theoretical Results

A numerical simulation was performed using the following parameters over a period of time $0 \le t \le 200h$.

Numerical Stability Analysis

Using the parameter values from [6] listed in the Table 2, steady points of the TIV model were determined mathematically below, as demonstrated in Table 3.

The local stability of each steady point was investigated by evaluating the eigenvalues of the Jacobian matrix $J(E_i), i = 0, \ldots, 4$, at the corresponding steady state. The steady point $(E_i), i = 0, \ldots, 4$, is locally asymptotically stable if all eigenvalues $\lambda_i, i = 1, .., 4$, have negative real parts. This further explains the oscillatory behaviour observed in the numerical simulations in the next subsection [13].

Time-Series Numerical Simulations

Numerical simulation using RKF 4(5) method with adaptive step-size was performed using a MATLAB ode45 solver [10]. In simulation, the solver was configured with relative tolerance $= 1 \times 10^{-1}$, absolute tolerance$= 1 \times 10^{-8}$, initial step size $= 0.01$ h, and maximum step size $= 0.5$ h. The TIV system was simulated over 200 h, with the initial conditions: $U_x(\mathrm{t} = 0) = 8 \times 10^5$ cells/mm^3, $U_y(t = 0) = 10^5$ cells/mm^3, $U_z(t = 0) = 6 \times 10^4$ cells/mm^3, $U_n(t = 0) = 4 \times 10^4$cells/mm^3, $U_v(t = 0) = 10^6$ virus/mm^3 [6].

Table2: Detailed description of the parameters of the TIV model

Parameter	Description	Range	Value
α	Rate of cancer cell proliferation	$0 < \alpha$	$2 \times 10^{-1}/h$
β	The rate at which cancer cells are infected by viruses	$0 < \beta$	7×10^{-8} mm^3/h/virus
k	The rate at which immune cells kill infected cells	$0 < k$	2×10^{-8} mm^3/h/immune cells
δ	Death rate of cancer cells that are infected by viruses	$0 < \delta$	1/18/h
s	Activation rate of immune cells by infected cells	$0 < s$	5.6×10^{-7} mm^3/h/infected cell
ω	Clearance rate of immunological cells	$0 < \omega$	2×10^{-12} mm^3/h/immune cell
P	Immunosuppressive medication	$0 < P$	0.5/h
μ	Trash clearance rate of cells that are dying	$0 < \mu$	1/48/h
b	The viral replication number at the time of death of the infected cancer cell	$0 < b$	50
k_0	Virus uptake rate by immune cells	$0 < k_0$	10^{-8} mm^3/h/immune cell
γ	Clearance rate of free virus	$0 < \gamma$	2.5×10^{-2} /h

In Fig (2), we notice that the uninfected cancer cells U_x begin with an initial value equal to 8×10^5 cells/mm³; then this number decreases rapidly from the first hour until it reaches zero at the seventh hour, which indicates that by $t = 7$ h, all uninfected cancer cells U_x had died, indicating 100% infection by the oncolytic U_v.

According to Fig (3), the infected cancer cells begin with a number $U_y(0) = 10^5$ cells/mm^3. These cells U_y reach a higher value in the first hour, which forms a peak, and then decrease until they reach zero. The increase and descent in the number of U_y represents the process of infection and death of cancer cells U_y as a result of oncolytic viruses U_v.

Fig (4) illustrates the behaviour of immune cells U_z, which begin with an initial value of 6×10^4 cells/mm³, then decrease, followed by increases, then ultimately decrease to zero cells by the end of the interval. Here, we can see a trough followed by a peak, indicating a decrease in immunity, followed by an increase in the number of U_z in the body, and the final decline to zero of immune cells U_z, indicating immune exhaustion with the treatment effect, resulting in a complete loss of immune cells U_z in the observed interval.

Here we notice from Fig (5) that the dead cells begin with an initial value of $U_n(0) = 4 \times 10^4$ cells/mm3, and the behaviour of the curve is sharp and continues to decrease in dead cells U_n until the end of the period, indicating that treatment effects combined with immune activity became effective early at the beginning of the interval. The rapid and continuous decline in dead cell density U_n suggests that dead cells are being cleared efficiently from the body of the individual.

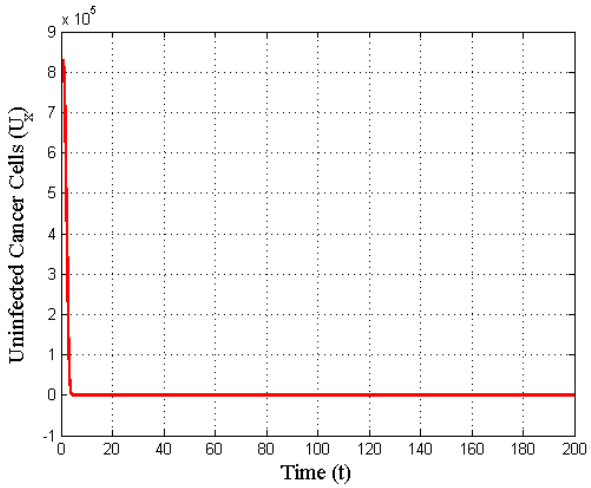

Figure 2: Dynamics of the density of uninfected cancer cells U_x

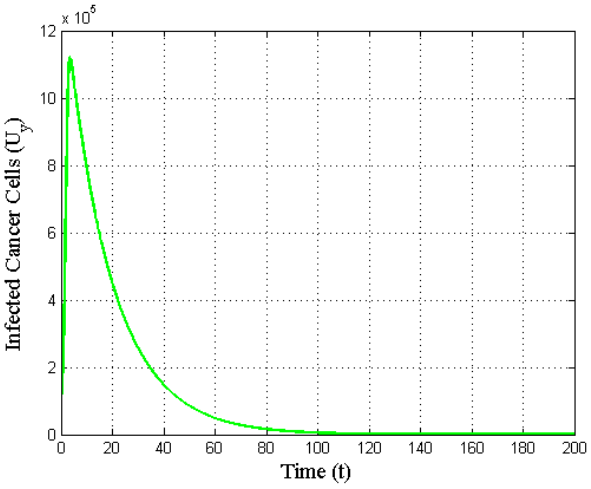

Figure 3: Dynamics of the density of infected cancer cells U_y

Fig (6) shows that the number of viruses starts at $U_v(0) = 10^6$ virus/mm³ and then rapidly grows. Initial growth indicates viral replication within infected cancer cells U_y. At the same time, the subsequent decline suggests depletion of susceptible cancer cells and immune clearance represented by the term $-k_0\, U_v\, U_z$, or natural viral decay represented by the term $-\gamma\, U_v$.

Table 3: Steady point of the TIV model

Steady points	U_x	U_y	U_z	U_n	U_v	Biological relevant	Stability
E_0	0	0	0	0	0	Yes	Unstable
E_1	0	0	-5×10^{10}	0	0	No	—
E_2	0	1.78×10^5	-2.78×10^6	0	-1.78×10^8	No	—
E_3	7142	25714	0	68571	2.86×10^6	Yes	Unstable
E_4	3.15×10^5	1.79×10^5	1.49×10^7	3.03×10^6	2.86×10^6	Yes	Unstable

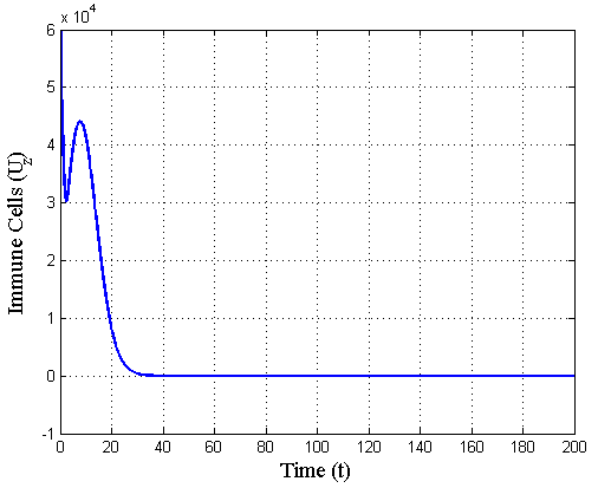

Figure 4: Dynamics of the density of immune cells U_z

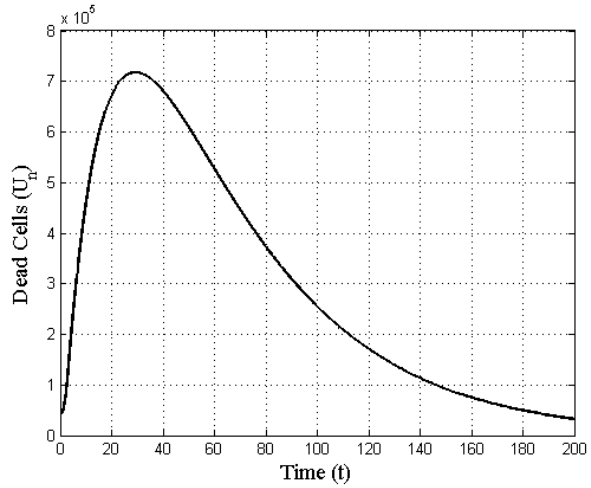

Figure 5: Dynamics of the density of dead cells U_n

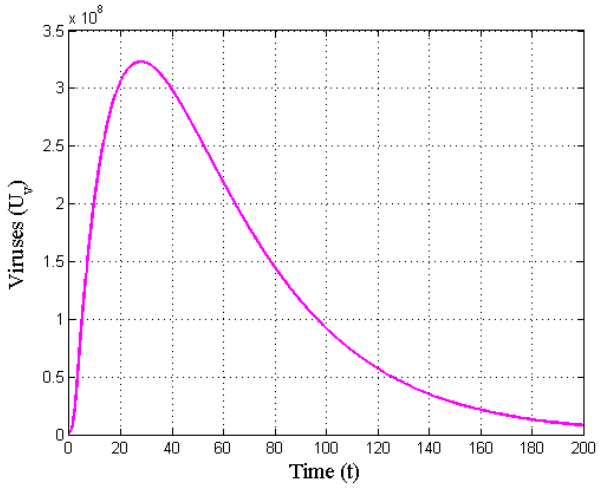

Figure 6: Dynamics of the density of viruses U_v

Biological Results

The numerical simulations contribute to the understanding of the biological behaviour of the TIV model, as the instability of biological steady points explains the rapid and fluctuating dynamics observed in the time-series simulations. The rapid decrease in the density of uninfected cancer cells U_x indicates an effective viral infection, while the peak and subsequent decline in the number of infected cancer cells U_y is explained by viral replication and cancer cell death. The immune cells demonstrate an initial trough followed by a peak, indicating a decrease in immunity, followed by activation, and finally, weakening. Furthermore, the decrease in the number of free virus U_v is consistent with the immune clearance of infected cancer cells. These results show the interaction between cancer cells U_y, the immune system U_z, and viruses U_v.

Conclusion

In this work, we study the effect of the combination of viral therapy and immune response on cancer cells. The Tumour–Immune–Virus model is a system of NODEs describing the interactions between uninfected cancer cells U_x, infected cancer cells U_y, immune cells U_z, dead cells U_n, and free virus particles U_v.

As part of the mathematical analysis, we proved the existence and uniqueness of system solutions (1) – (5), examined the positivity and boundedness of solutions, and examined the local stability of biologically relevant steady points. The system was analysed using linearization techniques and Lyapunov functions. As a result of these theoretical results, the TIV model is biologically consistent.

We used the numerical simulations in order to validate the analytical results, which have shown that combining viral immunotherapy has a clear effect, as it significantly reduces the density of cancer cells and enhances the immune response [2,17,18].

Future work

By incorporating spatial diffusion, response, and biologically motivated time delays, which extends the TIV model. It is in these situations that Computational Fluid Dynamics (CFD) can be used to simulate tumour growth, immune cell activity, and the spread of viruses [19].

Also, the proposed dynamical model can be combined with deep learning architectures for MRI-based tumour detection and classification [20]. A FPGA may also be a powerful tool for implementing iterative numerical schemes, such as Newton-Raphson, to improve computational efficiency [21].

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